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REPLY

We agree with Dr. Standing that a pediatric formulation of bosentan is needed. The pharmaceutical development of a pediatric formulation, in the form of an orodispersible tablet with a flexible dosage of 8 to 32 mg, is currently undergoing clinical evaluation in children in Europe and in the U.S.

However, during the course of development and validation of the pediatric formulation, the current adult formulation of bosentan was used to begin evaluation of the pharmacokinetics and safety of bosentan in children (1). We acknowledge that we do not describe in detail in our study (2) the technical aspects associated with cutting the adult tablets for the treatment of children. However, several studies have shown the adult formulation is suitable to this situation:

1. The active bosentan substance is uniformly spread throughout the bosentan tablet.
2. Seventy-five percent of the tablet weight is drug substance, thereby limiting the possibility of nonuniformity of the medication dose.
3. The weight of halved tablets, split with a commercially available tablet cutter, was within European and U.S. Pharmacopeia specifications (Actelion, personal communication, 2001). In addition, dissolution rates were measured and found to be similar for both whole and halved tablets.

Therefore, the use of split tablets was considered appropriate for conducting a pharmacokinetic study (1). Quartered tablets were not tested at that time. In our study (2), we followed the sponsor's recommendations of using a commercially available cutter to split the tablets, with no crushing of halved/quartered tablets, and direct oral administration.

Whereas the pharmaceutical development of the pediatric formulation of bosentan was ongoing, we treated children with symptomatic pulmonary arterial hypertension (PAH) at our clinics with the adult bosentan formulation following the sponsor's recommendation for dosing in children at that time (i.e., based on a conservative extrapolation by weight of the recommended adult dosages). Using this approach, these data demonstrated the safety and efficacy of bosentan for pediatric PAH. However, we also agree with Dr. Standing that pediatric dosing needs to be studied further. We anticipate that the current evaluation of a pediatric bosentan formulation will lead to optimal bosentan dosing regimens for children with PAH.

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Limitations of Crush Technique

Ge et al. (1) reported the results of a prospective study on long-term outcomes of "crush technique" (CT) with drug-eluting stents. This study raises, in our opinion, two main issues.

First, as pointed out by Williams and Abbott in their editorial (2), this study reports a clearly worse outcome as compared to studies with "provisional T stenting" (PTS) and serious concerns about safety profile (4.4% incidence of stent thrombosis). Moreover, the success rate in recrossing the stent struts for final kissing balloon is not reported in the study. Because 36% of patients did not undergo final kissing balloon postdilation, we may assume that, at least in some of them, it was not possible to recross the stent struts. This is an important limitation as any further therapy of side-branch restenosis in "unrecrossable" patients (40% incidence) becomes virtually impossible by means of percutaneous coronary intervention (PCI). From this perspective, PTS appears also to be superior as a second stent is needed in only 15% to 33% of cases, and final kissing balloon is possible in >95% of cases (3). Additionally, in case of side-branch restenosis it is always possible to perform additional PCI. Taken together these limitations may "crush" down the clinical role of CT, a conclusion not clearly underlined by the investigators.

Second, the modest results of CT reported in the study by Ge et al. (1) are not surprising. In fact, CT results in three drug-eluting stent (DES) layers crushed on an arterial wall at a site of high hemodynamic turbulence, with high chances of the stents' incomplete expansion where the coverage should be maximal. This